OPEN ACCESS
Freely Available Online

JOURNAL OF HEMATOLOGY AND ONCOLOGY RESEARCH
ISSN NO: 2372-6601

Review Article

DOI: 10.14302/issn.2372-6601.jhor-20-3372

Laboratory Tests Used in the Diagnosis of Immune Thrombocytopenia and General Treatment Approaches

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Abstract

Immune thrombocytopenia currently called under its' new name, immune thrombocytopenic purpura (ITP) is a disease characterized by thrombocytopenia, in which the body attacks its own platelets due to the disorders in immune system. The pathophysiology of this disease includes increased platelet destruction and most megakaryocyte production in bone marrow. The most common clinical manifestation of ITP is mild or severe progressive bleeding that could result in death. ITP is generally named as primary or secondary ITP according to thrombocytopenia severity, disease duration, bleeding status and secondary occurrence of the disease. Currently for diagnosis, despite the blood count, antiglobulin test and laboratory tests that can detect platelet-bound antibodies, they are not enough for definitive diagnosis. Like the difficulty in diagnosis, ITP treatment is quite complicated which varies depending on age, characteristics and risk of the patient. It is classified as first, second and third-line treatment options. Also, depending on the condition of patients, combined treatment might be an option which increases the complexity of the treatment. Unfortunately, discussions related to different clinical applications in diagnosis and treatments continue recently. For this reason, we considered that preparation of a review containing recent updates in diagnostic approaches and treatment options in ITP will be remarkable and beneficial for physicians interested in this subject.

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Citation: Fatih Ozcelik, Umran Keskin, Emrah Kılıçaslan, Ebru Kale (2020) Laboratory Tests Used in the Diagnosis of Immune Thrombocytopenia and General Treatment Approaches. Journal of Hematalogy and Oncology Research - 3(4):22-36. https://doi.org/10.14302/issn.2372-6601.jhor-20-3372

Keywords: Immune thrombocytopenia, Coombs Test, Thrombopoietin Receptor Agonists, Intravenous Immunoglobulin, Rituximab

Received: May 08, 2020 **Accepted:** May 27, 2020 **Published:** Jun 01, 2020

Editor: Rada M. Grubovic, Head of Department for Stem Cell Collection President of Macedonian Society for Transfusion Medicine, Macedonia.

Introduction

Platelets are the smallest shaped elements of the blood that play a primary role in preventing bleeding. One of the most common diseases associated with platelets is immune thrombocytopenia (ITP), an autoimmune disease, formerly called immune thrombocytopenic purpura. ITP is a disease in which autoantibodies attack the body's own platelets. These auto-antibodies, which are formed against antigens on the platelet surface, are formed as a result of a person's own tolerance disorder against their own platelet antigens due to disorders in the immune system. Although the pathophysiology of ITP is not yet fully understood, most important point is considered to be the production of antiplatelet auto-antibodies. Normally our immune system recognizes foreign organisms (bacteria, viruses, cancer cells and other foreign substances) and releases substances called antibodies against them. These antibodies form complexes by marking foreign organisms. Monocytes / macrophages recognize these complexes and destroy these marked complexes. In ITP, the immune system marks the surface antigens of platelets as foreign for an unknown reason. This situation leads to opsonization and disintegration of platelets in the organs (reticuloendothelial system) that form the body's defense mechanism, especially the spleen [1–3].

The incidence of ITP in adults is approximately 3-4 per 100.000 [4,5]. There are two important mechanisms in pathophysiology of the ITP. One is increased platelet destruction and the other is inadequate megakaryocyte production in bone marrow. The cause of platelet destruction is the formation of auto-antibodies targeting glycoprotein IIb/IIIa on the surface of the platelets, which occurs when immune system loses its tolerance to its platelet antigens. Marking platelets with these auto-antibodies causes them to be destroyed by macrophages or cytotoxic T cells. The decrease in megakaryocyte production is due to the dysfunction of megakaryocytes observed in ITP and insufficient levels of thrombopoietin (TPO), the main regulator of platelet production in megakoryocytes. Thus, an increase in platelet destruction and a decrease in platelet production are added[6–8]. The common clinical manifestation of this condition is bleeding. The most serious bleeding is intracranial hemorrhage, which can cause stroke and death.

General Approaches and Classification in ITP

Because ITP is developing due to a plasma protein (Ig or complement), some researchers administered ITP plasma infusion to healthy individuals in a study. After the procedure, they observed a sudden drop in platelet count and this finding was considered as an evidence of existence of auto-antibodies against platelets in ITP [9].

ITP might develop secondary to autoimmune diseases such as systemic lupus erythematosus and Hashimoto's thyroiditis, as well as due to some condition such as some cancers, immune system disorders, infections (hepatitis C virus (HCV), hepatitis B virus (HBV), human immunodeficiency virus (HIV), parvovirus, cytomegalovirus (CMV), helicobacter pylori infection, tuberculosis and brucellosis), vaccines, some medications, and pregnancy (Table 1). In these

Table 1. Secondary ITP causes

Autoimmune Disorders	Infections	Vaccinations	Drugs and pregnancy
SLE APS Hashimoto's thyroiditis Grave's disease Rheumatoid arthritis Evans syndrome	HIV HCV HBV CMV Rubella EBV Parvovirus H. pylori	Measles Mumps Rubella Varicella Hepatitis A Diphtheria Tetanus Pertussis	Quinine Heparin Fiban Abciximab Beta-lactam antibiotics Ristocetin Ticlopidine Clopidogrel

situations, the disease is called secondary ITP. As a matter of course, secondary ITP treatment mainly focused on resolving underlying causes, reducing platelet destruction and stimulating platelet production. If immune thrombocytopenia occurs alone, it is called primary immune thrombocytopenia or ITP. Primary ITP is a diagnosis of exclusion and accounts for 80% of all cases. ITP was previously used as an acronym for 'idiopathic thrombocytopenic purpura'. However, in 2009, Rodeghiero et al. prepared an international consensus report where they changed ITP as an abbreviation of immune thrombocytopenia on the grounds that most patients did not have purpura [2,10–15]. It was also emphasized that the diagnosis of primary ITP should be diagnosed in the first 3 months of the disease. The disease is called persistent ITP if it was diagnosed within 3-12 months from the onset of the disease, and chronic ITP after 12 months. Similarly, Provan et al. followed this nomenclature in their report on the investigation of primary ITP [16].

The course of ITP observed in children and adults is different and its treatment is also different. ITP is mostly chronic and more severe in adults. On the contrary, it is not usually chronic in children, it occurs acutely after an infection or vaccination and usually heals spontaneously. The ITP, which is seen as a child, generally heals within the first year. However, in some children the situation is different. There is no improvement and ITP becomes chronic. Treatment options should be reconsidered in these pediatric patients. Because, in addition to the side effects (weight gain, swelling of the face, flushing, fat accumulation in the trunk, thinning of the arms and legs, thinning of the skin, flushing, purple cracks in the abdomen, bone head aseptic necrosis, hypertension, tendency to fungal infections) associated with steroid use in children, growth retardation or slowing is added. For this reason, it should be tried not to use high dose for a long time especially in chronic ITP patients. In adults, ITP has a sneaky onset and the age of its appearance ranges from 30-60 years. Its incidence is almost equal in men and women [17–19]. In 2019, a document was published in which many researches and recommendations for ITP treatment were examined and evaluated. This final document provides recommendations on the diagnosis and management of ITP and quality of life assessments in adults, pregnancy and children [19].

Laboratory Methods Used in ITP Diagnosis

ITP is mostly detected incidentally by a hemogram test or bleeding story and low platelet count (thrombocytopenia) is the main finding. Thrombocytopenia may cause bleeding in mucous membranes (in mouth, lips, nasal mucosa and/or gingiva) and hematuria, melena, hypermenorrhea, petechia under the skin and rash in red-purple color following mild trauma. Although the normal platelet count range is considered as 150.000-450.000/mm3, the platelet count should be lower than 100.000/mm3 in order to descirbe it as thrombocytopenia. Because without falling below this number, there is generally no impairment in platelet functions and a bleeding diathesis. Excluding other causes of thrombocytopenia, this threshold is also used for the diagnosis of ITP. Spontaneous bleeding frequently observed in those with a platelet count lower than 30,000 / mm3. The presence of coexisting diseases (such as uremia and cirrhosis), use of some drugs (such as aspirin, heparin and warfarin), trauma, tooth extraction and surgical procedures increase the risk of bleeding [15–17,20,21].

In the case of thrombocytopenia, aggregates of the platelets could hardly form a functional plug. Accordingly, bleeding, especially after physical trauma, could take a long time and might be life threatening. Not every thrombocytopenia should be defined as ITP. Therefore, other diseases that may cause thrombocytopenia should be excluded before final diagnosis. In other words, patients should not have any complaint or finding other than bleeding during the diagnosic approaches. Primary ITP should not be a concern in the presence of symptoms such as fever, weight loss, sweating, abdominal distention, joint pain, skeletal abnormalities, mouth sores and jaundice. In the anamnesis and history, infectious and autoimmune diseases, viral and bacterial hepatitis and pregnancy that may cause secondary immune thrombocytopenia should be investigated. In addition, hereditary thrombocytopenia should be questioned while taking family history. Because when secondary causes disappear, platelet count will generally return to normal levels. Therefore, treatment strategy should be adjusted properly [15,16,20–22].

Some biochemical tests, viral infection screening, bone marrow examination and abdominal

ultrasonography may be required to confirm the diagnosis. In addition, there are specific tests today that detect anti-platelet autoantibodies that can be used in the diagnosis of ITP, as in autoimmune hemolytic anemia (AIHA). However, there is no ideal test for ITP yet [23]. Although there are many similarities between AIHA and ITP, anti-erythrocyte antibodies can be detected in the majority of AIHA patients with some simple methods (direct or indirect antiglobulin tests) [24,25], whereas platelet autoantibodies are much more difficult to detect. For this reason, there may be a contradiction in many ITP patients and definitive diagnosis can be quite challenging. As a general approach, severe thrombocytopenic response to intravenous immunoglobulin administration is a definitive indication of ITP. However, in many patients, the diagnosis may remain uncertain. Therefore, patients with a preliminary diagnosis of ITP should be investigated for underlying secondary causes of ITP and other causes of thrombocytopenia. Table 2 summarizes the strategy of approach in this regard.

Reticulated platelets and immature platelet fraction interpreted in favor of ITP can be detected with flow cytometry and automated blood count device. However, to a lesser extent, reticulated platelets and immature platelets can be detected in other thrombocytopenic diseases [26]. Coombs tests, which are widely used in the diagnosis of AIHA and Evans syndrome (coexistence of autoimmune hemolytic anemia and ITP), can also be applied in platelet antibodies. However, platelets cannot be isolated as easily as erythrocytes, they cannot be washed, and their numbers are relatively low. Therefore, investigation of platelets is much more difficult compared to erythrocytes. Despite all these disadvantages, Coombs tests used in the research of anti-platelet antibodies made important contributions to the understanding of ITP pathogenesis [9]. In direct methods used for this purpose, immunoglobulins (or complements) bound to the platelet surface are detected, just like in erythrocytes (Figure 1). In addition, radioactive labeled Coombs antiglobulin test, which can be used in the diagnosis and follow-up of immune thrombocytopenia in adults and children, can easily detect IgG and C3 bound to platelets [27]. The indirect method requires one more step than the direct method. Anti-platelet antibodies (or complement) in patients' serum are first incubated with platelet or platelet glycoproteins for a certain period of time, and then bound with Coombs antibodies [28]. In this method, trace amounts of thrombin can cause false positives because thrombin can activate platelets and

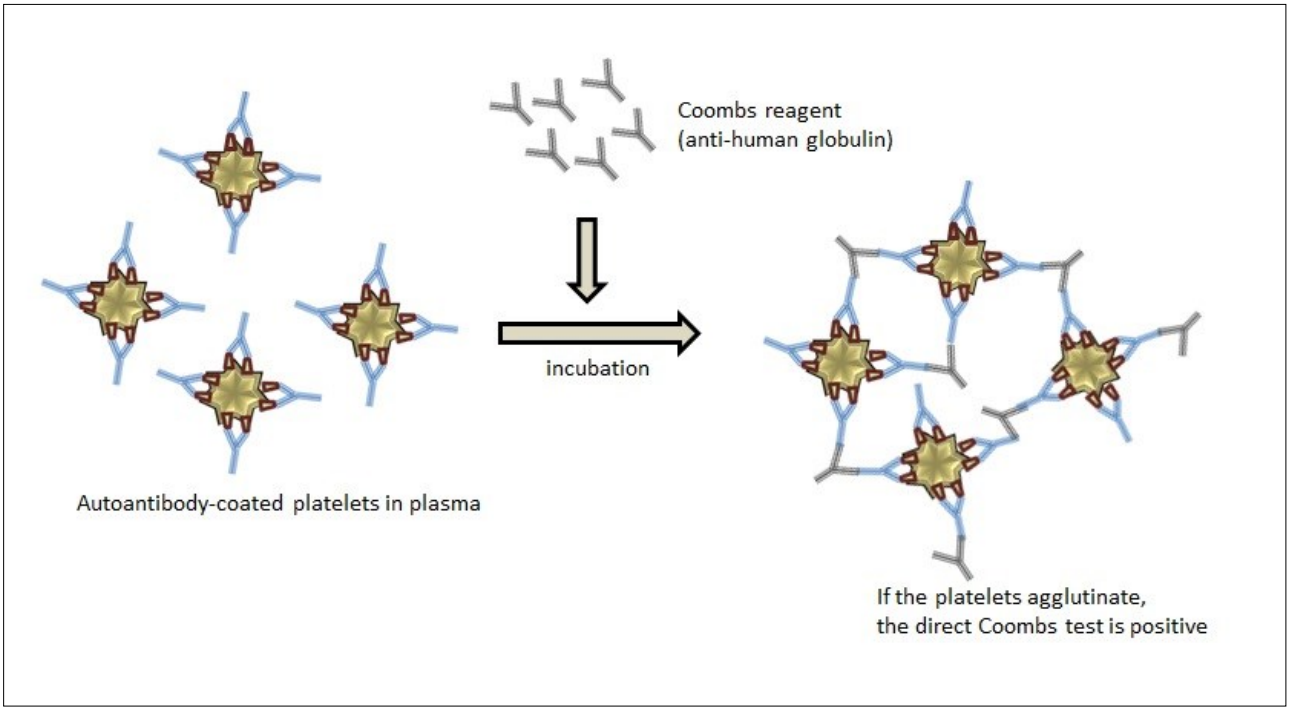

Figure 1. Detection of platelet antibodies by Coombs test

Table 2. Diagnostic approach in patients suspected of primer/seconder ITP

In the first step, evaluation of symptoms, history and physical examination	**In the second step, appropriate laboratory tests**	**In the third step, response to therapy**
Easy or excessive bruising	CBC, Reticulocyte count	IVIg
Petechiae, purpura	Peripheral blood smear	Oral steroid
Bleeding in the gum or nasal mucosa	HIV, HCV, HBV	Rituximab and thrombopoietin receptor antagonists
Blood in urine	Quantitative immunoglobulins	*Splenectomy
Unusually heavy menstrual bleeding	DAT	
Lymphadenopathy, and palpable liver or spleen	In adults, H. pylori tests (C14 urea breath test)	
Are there other causes of thrombocytopenia?	In age ≥60 years or haematological disorders, bone marrow test	
	MPV, electrolytes, liver and kidney tests, protein electrophoresis	
	Autoantibody tests related to autoimmune diseases (ANA, ANCA, Anti Tg etc.)	
	Further biochemical tests based on history and abdominal ultrasound (for splenomegaly etc.)	

This table is compatible with the International Consensus Report [16] and McMaster ITP Registry [87].

*The use of splenectomy has decreased with the emergence of the treatment option for rituximab and thrombopoetin receptor antagonists.

cause their clustering. Therefore, thrombin must be removed with additional procedures.

Today, different methods have been developed in which IgGs related to platelets are directly measured. In these methods, direct binding of labeled antibodies bound to platelet surface is detected by radioisotopes or flow cytometry. However, it should be remembered that most of the IgGs on the platelet surface are not pathological, and there are many IgGs in the alpha-granules in the platelet [29,30]. In addition, the methods that directly measure thrombocyte-bound IgGs showed similar positive results in almost all immune and non-immune thrombocytopenic disorders, which caused these methods to be questioned and overlooked. Today, there are a limited number of laboratories where these methods are used. Monoclonal antibody-specific immobilization of platelet antigens and enzyme-linked immunosorbent assay (ELISA) methods are the most common preferred methods to detect GP IIb/IIIa (where vWF and fibrinogen bind) and/or GP Ib/IX (where vWF connects) -specific autoantibodies on the platelet surface in patients with ITP [23,31]. Many laboratories researching ITP use these methods. However, these serological methods were found to have a high specificity and low sensitivity. In other words, although the positive determination of these tests can be interpreted in favor of ITP, they cannot be used as an exclusion criterion for ITP. However, there is evidence that the presence of antibodies against platelet glycoproteins can be used to predict the response to treatment [32–34].

Treatment Options of ITP

It is completely known that the immune system reactions in ITP is a pathological process in which autoantibodies are formed against platelet antigens due to impaired tolerance of their cell antigens. Based on this information, steroid, intravenous immune globulin (IVIg) and rituximab are used as important options in the treatment in order to silence or slow the immune reaction [23,35–38]. Fostamatinib, which has recently been approved, has started to be among the treatment options. However, all these treatments make a temporary improvement in patients. There is no definitive treatment; thus relapses (recurrences) are frequently observed. Among alternative treatments, splenectomy is considered as an important therapeutic alternative. Ineffective results from these approaches forced scientists to find different options. While discussing which treatment method is more successful, we also find it useful to provide ideas that can shed light on studies. The scientific world has not yet found a definitive answer to why the immune system loses the tolerance to its' tissue antigens. Therefore, more comprehensive investigations should be focused on this point. In our opinion, the most effective solution for all autoimmune diseases is to eliminate the source that will lead to the disorder.

Due to the high risk of morbidity and mortality, it is recommended to start ITP treatment in adults whose platelet count below 30,000 / mm3 and in patients with severe bleeding, regardless of platelet count. ITP's first-line treatment options include corticosteroids, IVIg, and anti-D immune globulin (in patients with Rh positive blood group) treatment. These options can quickly restore platelet count in emergency situations. However, these treatment options are not suitable for long-term treatment because of their limited response times and long-term toxicity. Their use also requires strict monitoring. Usually corticosteroid therapy is the first choice for the initial treatment of ITP due to its easy-to-apply and low cost [15,39,40]. However, IVIg therapy, which can increase the number of platelets more rapidly, should be preferred in patients with active bleeding. Increased platelet count is expected within the first 24-48 hours of corticosteroid treatment.

Corticosteroids

The main purpose of the use of corticosteroids in ITP is to reduce antibody production by immunosuppression and prevent platelet destruction by macrophages / monocytes. However, it should be remembered that these drugs have serious side effects. For this purpose, prednisone, prednisolone, methylprednisolone and dexamethasone, which are medium and long-acting steroids, are used. In the treatment of ITP, prednisone, prednisolone, methylprednisolone and dexamethasone are used [40,41]. The most common approach is the use of oral prednisone at a dose of 0.5-2.0 mg / kg for 2-4 weeks, followed by 40 mg / day dexamethasone 4 days a week for 2 - 4 weeks with 1-4 cycles. In a study comparing the efficacy and reliability of treatment with high-dose dexamethasone and prednisone in patients newly diagnosed ITP, a group of patients was administered 40

mg dexamethasone per day for 4 days or 1 mg / kg prednisone per day for four weeks. The initial response of dexamethasone (reaching the platelet count greater than 30,000 / mm3) was faster than prednisone. However, there was no difference between them in terms of continuous response (reaching a platelet count greater than 30,000 / mm3 for six months) [41]. Unfortunately, long-term corticosteroid therapy has several important side effects such as osteoporosis, diabetes, hypertension and weight gain. For this reason, they should be avoided as much as possible and the patients should be followed closely if their use was mandatory. If there is not an enough response with corticosteroids, IVIg is recommended as a second-line therapy. The same approach can be applied in patients who cannot tolerate the side effects of corticosteroids [42].

Intravenous Immunoglobulin

The main purpose in the use of IVIg therapy is to shut down the Fc receptors in the reticuloendothelial system, where platelet destruction occurs, to prevent the destruction of labeled platelets by phagocytes. The standard IVIG dose has been reported to be 400 mg/kg/ day for 5 days. The most guidelines currently recommend administering a single dose of IVIg (1 g/kg), which can be repeated depending on the platelet response. However, IVIg treatment is temporary and some side effects may occur; IVIg administration is generally well tolerated. Headaches, chills, arthralgia, back pain and rarely occurring kidney injury are the most common side effects [13,20,43,44]. The risk of kidney injury can be reduced by adequate hydration before IVIg administration.

Anti-D Immunglobulin

Anti-D immunoglobulin therapy has been used for the treatment of immune thrombocytopenia in non-splenectomized Rh-positive patients and this treatment was approved by the Food and Drug Administration (FDA). IVIg prepared from the plasma of immunized Rh-negative human donors can be used as an alternative for patients with Rh-positive blood type. The goal of this treatment is to neutralize the binding of autoantibodies to platelets and block the macrophage system. The purpose of this treatment is to block the macrophage system by neutralizing the binding of autoantibodies to platelets. The recommended dose for anti-D immune globulin ranges from 50-75 µg / kg intravenously at one time. The side effects of anti-D immune globulin therapy are similar to those of IVIg. Fatal inravascular hemolysis cases have also been reported. Because of these serious side effects, patients receiving anti-D immune globulin should be monitored for at least eight hours for signs of inravascular hemolysis and other side effects [45–47].

Splenectomy

Second and third-line treatments should be applied to patients with permanent and chronic ITP who have a high risk of bleeding that does not require emergency or rescue treatment. While rituximab is recommended as the second-line treatment at this stage, splenectomy is recommended in the third-line treatment. While splenectomy was among the second-line treatment options, it was replaced in the third-line treatment due to the effective novel treatments that emerged with TPO receptor agonists (eltromobopag and rhomiplasty) [48–50]. Therefore, splenectomy is considered an option following unsuccessful steroid and rituximab treatment. In addition, the response rate of the patients to splenectomy (especially higher in young patients) is 2/3, which is actually the answer to why it should be in third-line [40,51,52]. In cases where a certain response cannot be obtained with monotherapies, second and third-line treatments could also be considered in combination. Splenectomy decision should be considered well because it is necessary to allow spontaneous or treatment-related remissions to occur. Therefore, splenectomy should be postponed until 12 months after the diagnosis of ITP, especially in children and elderly patients with high surgical morbidity [53,54].

In general, splenectomy is considered as an effective therapeutic option in ITP, but it has significant complications. One of the most important complications of splenectomy is bleeding during the procedure. Other complications include venous thromboembolism, pneumonia, and other infections. Splenectomy-related mortality rate is lower in laporoscopy compared to open laparatomy (1% and 0.2%, respectively) [51,55,56]. In addition, relapses can be observed after splenectomy. Therefore, radiographic evaluation should be performed for the possibility of accessory spleen. As a hope, immunosuppressive treatment trials are among the options in cases where there is no response to

splenectomy. These immunosuppressive agents include cyclophosphamide, azathioprine, cyclosporine and vincristine. In later stages, use of plasmapheresis, androgens (danazol), colchicine and dapson may be on the agenda [57–59].

Thrombopoietin Receptor Agonists

It has been reported that TPO-receptor agonists (eltrombopag, romiplostim and avatrombopag), a class of platelet growth factors, can be used in patients with chronic ITP who responded poorly to corticosteroids, immunoglobulins, and splenectomy. TPO-receptor agonists induce platelet production by activating JAK2 and STAT5 kinase pathways through TPO receptors on megakaryocytes. Megakaryocytes induced in this way will have longer lives and produce more platelets. Thus, they reverse the production defect that creates a ground for ITP [1,13,60–63]. Besides immunosuppressive, immunomodulating agents and splenectomy, TPO-receptor agonists is a new option and limited to patients with chronic ITP who failed with glucocorticoids, splenectomy and IVIg [15,63]. However, the use of these agents is common in patients with acute or persistent ITP, and the use as a first-line is still under investigation [64]. In order to provide optimal benefit with TPO-receptor agonists in treatment-resistant ITP patients, it is necessary to know how to use, dosage, duration and side effects in all treatment steps and combination therapy because the decision to administer a TPO-receptor agonist after an immunosuppressive therapy and splenectomy may be complicated. In general, TPO-receptor agonists that require long-term use have a higher clinical response rate (~ 80%) than second and third-line treatment agents [65]. It is commonly observed that ITP patients with lower TPO levels better respond to TPO-receptor agonists [66,67]. It is also thought that TPO levels can be used to guide the treatment. It was found remarkable that in patients who have not used TPO-receptor agonists and had splenectomy, a response rate up to 50% has been observed, and a limited number of patients developed intolerance (tachyphylaxis) to the commercial dose of TPO-receptor agonists [68–70]. In second-line therapy, rituximab and then splenectomy are seen as an alternative to TPO-receptor agonists [71]. However, in many clinical applications, it is considerable to use medical treatments for at least 1 year before considering splenectomy in most adults.

Romiplostim is a subcutaneous peptide that administered once a week. In order to get sufficient response to Romiplostim (platelet number is ≥50.000 / mm3) 1-2 µg / kg / week starting dose is sufficient and treatment is continued with 1µg / kg every week [72]. It is reported that in patients with acute bleeding symptoms and refractory disease despite glucocorticoid and IVIg, romiplostime can be started at higher doses in order to obtain more prudent and effective results in a shorter time [73]. With the classical approach, the gradual increase in the dose of romiplostim may cause deep thrombocytopenia and bleeding risk in a long time, while a faster dose increase may result in thrombocytosis (risk of thromboembolism).

Eltrombopag and avatrombopag are small molecule TPO-receptor agonists that can be administered orally once a day. The recommended starting oral dose of Eltrombopag is 50 mg per day under fasting. The initial dose of eltrombopag is 25 mg in patients with chronic liver disease and in children aged 1-5 years [62,63,74]. It is used in higher doses (150 mg/day) in aplastic anemia. However, there is not reliable data to support its use at this level in patients with ITP. In alternate intermittent dosing, the dose of 75 mg is usually used 1-5 times a week instead of the daily dose, due to the long half-life of the eltrombopag (26-36 hours). In patients receiving romiplostim or eltrombopag, it is recommended to reduce the drug dose when the platelet counts reach a level greater than 400,000 / mm3. Eltrombopag is potentially hepatotoxic [75]. Therefore, it should not be used in patients with ITP and chronic liver disease, as it will increase the risk of venous thromboembolism (VTE).

Avatrombopag is not yet approved for use in ITP treatment. Therefore, there are no general dosage recommendations. However, in phase II studies, it is reported that a daily dose of 5-10 mg/day creates an adequate platelet response in approximately ½ of patients, and a dose of 20 mg/day in 80% of patients [76].

Rituximab

CD19, CD20 and CD22 are antigens that are not expressed in non-lymphoid cells and expressed on the surface of all B cells CD19 antigen is also expressed by follicular dendritic cells. Therefore, the CD20 antigen is considered an antibody dependent antitumor target. The

rituximab, a monoclonal anti-CD20 antibody produced for this purpose, is commonly used in non-Hodgkin lymphomas. The basic approach in Rituximab therapy is to prevent B cells from producing autoantibodies. FDA approved its use in the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis. However, since the studies are not finished, there is no approval yet for the use of rituximab in ITP. It is recommended that IVIg can be used in patients with high risk of bleeding that has failed with the treatment of anti-D immune globulin and corticosteroids. The recommended dose of rituximab in ITP is 375 mg/m2 once a week for four weeks [1,40,77–80]. In adults with chronic disease and ITP, the platelet response of rituximab has been reported to be approximately 60%, especially in women and patients under 40 years of age. Its use was found to be limited in emergency and acute conditions. It has also been observed that rituximab is associated with some side effects such as fever, allergic skin rashes, tremors, and vomiting.

Fostamatinib

Fostamatinib is an oral inhibitory agent (Moore) of spleen tyrosine kinase (Syk), which is expressed by hematopoietic cells and plays an important role in the destruction of platelets by Fc-receptor activation [81]. Syk signaling pathway is the center of phagocytosis-based antibody-mediated platelet destruction in adults with ITP. In two different studies conducted in 2018 and 2019, it was found that approximately 30% of patients using phosphatimib received a platelet response (platelet count ≥ 50 000 / μL) within the first 12 weeks of treatment. Although generally well tolerated, some non-permanent side effects of this treatment have been observed, such as diarrhea, hypertension, nausea, dizziness and increased liver function tests. In this multicenter study, it was found that the treatment of fostamatinib showed significant success even in those who failed splenectomy, thrombopoietin agonist and rituximab treatment [82,83]. Co-administration of phosphomatinib, which is mainly metabolized via the Cytochrome P450 3A4 pathway in the liver and intestine, with Cytochrome P450 3A4 inhibitors or inducers, which use the same metabolic pathway, can change the effects of fostamatinib [81]. Therefore, it should be used carefully.

Fostamatinib has been approved in the U.S. for use in adult patients with chronic ITP who have responded poorly to a previous treatment [84]. However, there is still insufficient experience in its use. Therefore, we think that it will be useful to continue the research.

Criteria for Confirming ITP Diagnosis and Treatment

In the light of all the abovementioned evaluations and literature reviews, we prefer to say that there is still no single laboratory test that can be alone for the definitive diagnosis of ITP. Therefore, the diagnosis should be made with both clinical and laboratory evaluations. Attention should be paid to pseudothrombocytopenias, which may lead to an incorrect diagnosis of ITP. In order to discriminate the true pseudothrombocytopenia from thrombocytopenia, the use of other anticoagulated (sodium citrate, oxalate and heparin) tubes instead of EDTA tubes, bringing the blood to 37 °C, determining the platelet aggregation under the microscope or using the kanamycin added blood samples [85,86]. The presence of thrombocytopenia, exclusion of other causes, detection of anti-platelet autoantibodies and increase in the number of platelets in response to treatment (steroid, IVIg, and secondary causes) should be the criteria to be used for definitive diagnosis [23,35–37]. However, a relatively lower sensitivity of the methods for the detection of anti-platelet autoantibodies and their inability to exclude ITP make other two suggestions more valuable in the diagnosis.

Steroids remain important as a first-line therapeutic option in clinical practice. Rituximab and TPO-receptor agonists with limited side effects, which are alternatives to IVIg, anti-D immune globulin and splenectomy, are highly effective therapeutic option in the management of ITP. When choosing the first- (corticosteroids, IVIG and anti-D immune globulin), second- or third-line treatment options mentioned above, the patients' bleeding risk should be considered, and an individual treatment algorithm should be planned. Treatment of patients with mild ITP might begin with corticosteroids as a general approach. IVIg therapy (as an alternative, anti-D immune globulin) should be reserved for the patients with severe bleeding and / or those who do not develop enough response to corticosteroids. In patients with treatment-resistant and non-urgent chronic ITP, splenectomy and rituximab are the recommended options. Furthermore, TPO-receptor agonists can also be considered as an additional therapy

in the treatment of chronic ITP. Beyond all these therapeutic options, combined treatment should not be also ignored.

Conclusion

In conclusion, both the clinical and laboratory evaluation seems to be the only solution in the diagnosis of ITP. Thrombocytopenia and platelet response to treatment continues to be the most effective diagnostic criteria. There is no specific treatment pattern for ITP. The treatment in ITP continues to be a complicated that uses different options from monotherapy to combined therapy and adjusted according to the patients' conditions.

Abbreviations

SLE: Systemic lupus erythematosus

APS: Antiphospholipid syndrome

HIV: Human immunodeficiency virus

HCV: Hepatitis C virus

HBV: Hepatitis B virus

CMV: Cytomegalovirus

EBV: Epstein-Barr virus

H. Pylori: Helicobacter pylori

ITP: Immune thrombocytopenia

IVIg: Intravenous immunoglobulin

CBC: Complete blood count

HBV: Hepatitis B virus

HCV: Hepatitis C virus

Human immunodeficiency virus

DAT: Direct antiglobulin test

MPV: Mean platelet volume

ANCA: Antineutrophil cytoplasmic antibody

ANA: Antinuclear antibody

Tg: Tyroglobulin

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